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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,781	10/19/2005	Ekaterina Vladimirovna Barsova	U 015759-8	6930

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EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
10/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,781	BARSOVA ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *25 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 19-27* is/are pending in the application.

4a) Of the above claim(s) *9-11,14-16 and 19-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,12-13,17,27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05/04/05* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/2005;11/2005;*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group II, claims 1-8,12-13,17 and 18 in the reply filed on 06/25/2008 is acknowledged. The traversal is on the ground(s) that the claimed invention is directed to specific nucleic acid molecules with structure defined by the recited SEQ ID NO:s, which structure imparts different properties to the proteins encoded. Applicant argues that the Examiner may gave been reading the terms "derivatives", "mimetics" and "mutants" so broadly as to read on the prior art and that the claims have been amended to no longer read on such. This is not found persuasive because variants of the same gene have been included in a single Group. The basis of the lack of unity lies in the special technical feature common to each Group being a gene encoding a fluorescent protein, which is not a contribution over the prior art. The cited art in the lack of unity requirement is not cited as prior art over the claim but established the common special technical feature amongst the Groups to have already been known in the art. Applicant argues that ppluGFP (Group I) is similar to ppluGFP2 (Group II). This argument is not persuasive as the products are distinct and separate and the common technical feature is not a contribution over the prior art. The common special technical must be a contribution over the prior art for unity to exist. In the instant case, it is not.

The requirement is still deemed proper and is therefore made FINAL.

Claims 9-11,14-16,19-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 06/25/2008.

Claims 1,6-8,13,17 are amended. Claim 18 is cancelled. Claim 27 is added. Claims 1-17,19-27 are pending. Claims 9-11,14-16,19-26 are withdrawn. Claims 1-8,12-13,17 and 27 are under consideration in the instant office action.

Claim Objections

Claim 1objected to because of the following informalities: The term "which" in line 3 should read "that". Appropriate correction is required.

Claim 6 objected to because of the following informalities: The term "hose" in line 2 should read "host". The term "Claim" in line 3 should not be capitalized. Appropriate correction is required.

Claim 7 objected to because of the following informalities: The term "chromosonal" in line 2 should read "chromosomal". Appropriate correction is required.

Claim 27 objected to because of the following informalities: The term "chromosonal" in line 2 should read "chromosomal". The claim also lacks appropriate punctuation at the end of the claim. Appropriate correction is required.

Specification

The disclosure is objected to because of the following informalities: The description of Figure 1 at page 4 must include a sequence identifier for the sequence depicted in Figure 1.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-8,12-13,17 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule selected from the group consisting of a) a nucleic acid that encodes a protein comprising the amino acid sequence as shown in

SEQ ID NOs: 4,18,20,22,24,26, or 28 b) a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NOs: 3,17,19,21,23,25, or 27 and c) a nucleic acid that differs from a nucleic acid of b) due to the degeneracy of the genetic code and cells and vectors comprising said nucleic acid, does not reasonably provide enablement for other claimed embodiments embraced by the breadth of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims encompass nucleic acids encoding ppluGFP2 and a number of variants that encode mutated forms of ppluGFP2 with various beneficial characteristics. The claims also encompass fragments of these nucleic acids as well as any nucleic acid having as little as 70% nucleic acid identity to the claimed SEQ IDs or those that encode proteins with as little as 80% sequence identity.

The specification teaches a number of variant that are specifically mutated at specific residues to optimize the encoded proteins. The specification teaches using mammalian-optimized codons as well as yeast-optimized codons (page 22) and used random mutagenesis to generate a cyan emitting protein as well as alter maturation speed and brightness. The specification also teaches a variant that has a lesser tendency to form aggregates. However, the specification does not teach the broad genus of fragments and nucleic acids that hybridize to either the claimed full length sequences or fragments.

The specification contemplates using nucleotide sequences that hybridize under stringent conditions to the nucleotide sequences comprising SEQ ID NO: 3,17,19,21,23,25,27 or 29 or nucleic acids that otherwise encode the same proteins as SEQ ID NO:3,17,29,21,23,25 or 27. In view of the state of the art and the lack of guidance provided by the specification for what conditions are considered stringent, it is not apparent to one skilled in the art if any of nucleic acid sequence, which hybridizes under any condition, including those considered to be most stringent, would possess the same biological activity compared to SEQ ID NOs: 4,18,20,22,24,26 and 28. The relationship between a sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Chiu et al., *Folding and Design*, 1998, pp. 23-228). The structural identity of sequences isolated by their hybridization properties is unpredictable in relation to the original sequence to which it hybridized. Kennell teaches that 25 to 50% nucleic acid identity is all that is necessary for hybridization of a sequence under any conditions and that obtaining non-specific hybridization products are highly common in the art (*par bridging p. 260 and 261 and par 1 of p. 261*). The specification provides general guidelines and conditions for obtaining hybridization products. However, these conditions are exemplary and not limiting. The general guidelines and conditions provided by the specification do not provide any guidance to overcome the unpredictabilities described in the art. Furthermore, the state of the prior art as exemplified by Wallace et al. (*Methods Enzymol, Vol. 152, pp. 432-443, 1987*) and Sambrook et al. (*Molecular Cloning, 2nd Edition, 1989, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, p.*

11.47) is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide is unpredictable. Furthermore, the as-filed specification does not provide sufficient guidance to determine the structural and functional limitations of a nucleic acid probe which hybridizes specifically to the DNAs of SEQ ID NO: 3,17,19,21,23,25 or 27 under any stringent condition wherein said stringent hybridization conditions prevent said nucleic acid probe from hybridizing to DNA other than SEQ ID NO: 3,17,19,21,23,25 or 27. The lack of working examples in view of the prior art and the specification would result in an undue amount of experimentation for one skilled in the art to reasonably correlate any DNA probe that would meet the structural limitations of the claimed embodiment to a functional use. Thus, one of skill in the art would not know how to use a protein encoded by a sequence that merely hybridizes to SEQ ID NO:3,17,19,21,23,25 or 27.

The claims encompass nucleic acid fragments of SEQ ID NO: 3,17,19,21,23,25 and 27 as well as nucleic acids with at least 70% sequence identity to any of those fragments. The claims encompass proteins with at least 90% amino acid identity to SEQ ID NOs: 4,18,20,22,24,26 or 28. The level of experimentation to determine which of the fragments or protein variants would encode or have the desired and useful activity would be undue.

The functional domains necessary and sufficient for the luminescent activity is not disclosed, an artisan would not know which sequences would need to be conserved to render the equivalent biological function as claimed. An artisan would not know which 10% of the sequence could be different from polypeptide sequence of SEQ ID NO: 4,18,20,22,24,26 or 28 and still retain the necessary function.

One skilled in the art would have to make and test with further experimentation an enormous number of nucleic acids that meet the structural limitations and determine how to use them.

Claim 7 is drawn to a cell comprising the expression cassette of claim 6. The claim encompasses both isolated cells in vitro as well as cells transfected *in vivo*. Thus, the claims read on a cell of an animal that comprises one of the claimed nucleic acids. The specification teaches isolated cells, in vitro, that

express the claimed nucleic acids and uses therefore. However, the specification, while contemplating transgenic animals expressing the claimed nucleic acids (see page 14), it does not teach and describe any animal with one or more cells comprising or expressing the claimed nucleic acids. While one of skill in the art could reasonably make such an animal encompassed by the claims, the specification fails to provide the guidance necessary to determine what properties the animal would have and, accordingly, how it would be used. Thus, the specification is not enabling for the in vivo embodiments of the claims because it would require an undue experimentation to determine how to use the in vivo embodiments of the claims.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8,12-13,17-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "hybridizes under stringent conditions" in claim 1(c) is a relative phrase, which renders the claim indefinite. The phrase “hybridizes under stringent conditions" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The definition of the phrase “hybridizes under stringent conditions” is not a closed definition from reading page 6 in the as-filed specification. The parameters of what constitutes moderately or highly stringent conditions are not defined by the claims.

Claim 1 recites the limitation "the nucleotide sequence" in lines 11-12 and line 18. There is insufficient antecedent basis for this limitation in the claim. The antecedent basis is unclear as multiple sequences are recited in the claim.

Claim 6 recites the limitation "the nucleotide sequence" in line 2. There is insufficient antecedent basis for this limitation in the claim. The antecedent basis is unclear as multiple sequences are recited in parent claim 1.

Claims 2-8,12-13,17-18 depend from claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1,5,6,7,8,17,27 are rejected under 35 U.S.C. 102(b) as being anticipated by Pekarsky (1998, PNAS, 95:8744-8749) as evidenced by GenBank AF069958.

Claim 1 broadly encompasses fragments of the nucleotide sequences set forth in SEQ IDs:3,17,19,21,23,25 or 27. The claim also encompasses nucleic acids that will hybridize to any of these fragments and nucleic acids that have at least 70% identity to any of such fragments.

Pekarsky taught COS cell line comprising an expression vector encoding Nit1. Nit1 has a span of nucleic acids identical to nucleotides 3-18 of SEQ ID NO:3 (see attached alignment).

Claims 1,5,6,7,8,17,27 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by US 7157566 (filed April 2002; published March 2003).

Support for the teachings of SEQ ID NO:3 and 4 are not found in US Provisional Application 60/36857. Support for SEQ ID NO:3 and 4 is found in 60/459679, filed 04/02/2003. Support for SEQ ID NO:17-28 is not found in either provisional application. However, to the extent that the claims are not limited to SEQ ID NO:3 or 4, the effective filing date for the claimed subject matter is the filing date of priority document PCT/RU03/00525, filed 11/26/2003.

Claim 1 broadly encompasses fragments of the nucleotide sequences set forth in SEQ IDs:3,17,19,21,23,25 or 27. The claim also encompasses nucleic acids that will hybridize to any of these fragments and nucleic acids that have at least 70% identity to any of such fragments. Dependent claims are drawn to expression vectors and cells comprising the claimed sequences.

'566 taught SEQ ID NO:7, which is 73.4% identical to a region of SEQ ID NO:3 (See alignment below. '566 also taught expression vectors and cells comprising the sequence.

```
; PATENT NO: 7157566
; GENERAL INFORMATION:
;  APPLICANT: Tsien, Roger
;  APPLICANT:  Campbell, Robert
;  TITLE OF INVENTION: MONOMERIC AND DIMERIC FLUORESCENT
;  TITLE OF INVENTION:  PROTEIN VARIANTS AND METHODS FOR MAKING SAME
;  FILE REFERENCE: UC083.1CP2CP1
;  CURRENT APPLICATION NUMBER: US/10/121,258
;  CURRENT FILING DATE:  2002-04-10
;  PRIOR APPLICATION NUMBER: 09/794,308
;  PRIOR FILING DATE: 2001-02-26
;  PRIOR APPLICATION NUMBER: 09/866,538
;  PRIOR FILING DATE: 2001-05-24
;  NUMBER OF SEQ ID NOS: 78
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 7
;   LENGTH: 681
;   TYPE: DNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Polynucleotide encoding DsRed polypeptide variant
;   OTHER INFORMATION: "dimer2"
JS-10-121-258-7

  Query Match             7.3%;  Score 73.4;  DB 5;  Length 681;
  Best Local Similarity   48.4%;  Pred. No. 5.2e-10;
  Matches  296;  Conservative    0;  Mismatches  306;  Indels    9;  Gaps    3;

Qy         47 CATGAAGATTGAGTGCCGCATCACGGGAACCCTGAACGGAGTGGAGTTTGAGCTGGTCGG 106
               ||||    |  ||   |||||   |||  || |||||||    ||||| ||| | |  ||
Db         36 CATGCGCTTCAAGGTGCGCATGGAGGGCTCCGTGAACGGCCACGAGTTCGAGATCGAGGG 95

Qy        107 AGGTGGAGAAGGGACTCCTGAGCAGGGACGTATGACCAACAAGATGAAGTCTACCAAGGG 166
                |  || || ||    ||  |  ||||      ||||  |||| |||||    ||||||||
Db         96 CGAGGGCGAGGGCCGCCCCTACGAGGGCACCCAGACCGCCAAGCTGAAGGTGACCAAGGG 155

Qy        167 CG---CCTTGACCTTCTCCCCCTACCTTCTCTCTCATGTCATGGGATACGGGTTCTACCA 223
              ||   || || ||||| ||     || | || || |      |    ||||| | | |
Db        156 CGGCCCCCTGCCCTTCGCCTGGGACATCCTGTCCCCCCAGTTCCAGTACGGCTCCAAGGC 215

Qy        224 CTTTGGTACCTATCCCAGTGGGTATGAGAATCCCTTCCTGCATGCCATCAACAACGGGGG 283
               |  |  |   | |||   |       |   |     ||   || ||  | | ||
Db        216 GTACGTGAAGCACCCCGCCGACATCCCCGACTACAAGAAGCTGTCCTTCCCCGAGGGCTT 275

Qy        284 GTACACCAACACCAGGATTGAGAAGTATGAGGATGGAGGAGTTCTTCATGTTAGCTTTAG 343
               |    |   |  |||   ||| |  ||||| || || ||  |     || | |
Db        276 CAAGTGGGAGCGCGTGAT---GAACTTCGAGGACGGCGGCGTGGTGACCGTGACCCAGGA 332

Qy        344 CTACAGATATGAAGCAGGCAGGGTGATTGGGGATTTCAAGGTTGTCGGGACAGGATTCCC 403
               || |       | |  |||| | ||||     |  | ||| |   ||| ||    |||||
Db        333 CTCCTCCCTGCAGGACGGCACGCTGATCTACAAGGTGAAGTTCCGCGGCACCAACTTCCC 392

Qy        404 TGAGGACAGTGTGATCTTCACCGACAAGATCATCCGGTCCAATGCTACCGTGGAGCACTT 463
               ||| | |   |  |     | |||| |||  | |     | ||  ||     |||| | |
Db        393 CCCCGACGGCCCCGTAATGCAGAAGAAGACCATGGGCTGGGAGGCCTCCACCGAGCGCCT 452

Qy        464 GCACCCAATGGGAGACAACGTTCTTGTGGGCTCCTTCGCGAGAACCTTTTCCCTGAGGGA 523
               | ||||     | |||  ||| ||   ||||     ||        || |    |||| |||
Db        453 GTACCC---CCGCGACGGCGTGCTGAAGGGCGAGATCCACCAGGCCCTGAAGCTGAAGGA 509

Qy        524 TGGAGGCTACTACTCATTTGTGGTTGACAGCCACATGCACTTCAAGAGTGCCATCCACCC 583
               || ||| ||||||    | | | |  | | | |  |          |||||   || | | |
Db        510 CGGCGGCCACTACCTGGTTGAGTTCAAGACCATCTACATGGCCAAGAAGCCCGTGCAGCT 569

Qy        584 ATCCATCCTCCAGAACGGGGGGCCCATGTTTGCCTTCAGGAGAGTTGAGGAACTTCACTC 643
                 ||  |  | |  ||| ||   ||| | | | | |||          | ||      || |
Db        570 GCCCGGCTACTACTACGTGGACACCAAGCTGGACATCACCTCCCACAACGAGGACTACAC 629

Qy        644 CAACACTGAAC 654
               || |   ||||
Db        630 CATCGTGGAAC 640
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Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio/
Primary Examiner
Art Unit 1632